Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction

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Table 1. Characteristics of the BIOSTAT population

Variables	Baseline				Changes between Baseline and 9 months					
	All (N=1325)	No MRA (N=584)	MRA (N=741)	p	All (N=1049)	MRA at both visits (N=494)	MRA discontinuation (N=91)	MRA initiation (N=168)	No MRA (N=293)	p for trend
Age, years	66.1 ± 12.2	68.2 ± 12.2	64.4 ± 12.0	<0.001	65.4 ± 12.2	63.6 ± 11.9	65.7 ± 12.4	64.6 ± 12.4	68.9 ± 12.0	<0.001
Male gender, n (%)	1027 (77.5)	433 (74.1)	594 (80.2)	0.009	811 (77.3)	393 (79.6)	71 (78.0)	130 (77.4)	215 (73.4)	0.25
White caucasian, n (%)	1305 (98.5)	579 (99.1)	726 (98.0)	0.083	1035 (98.7)	484 (98.0)	91 (100.0)	166 (98.8)	291 (99.3)	0.26
Southern Europe countries, n (%)	775 (58.5)	263 (45.0)	512 (69.1)	<0.001	603 (57.5)	345 (69.8)	59 (64.8)	81 (48.2)	115 (39.2)	<0.001
BMI, kg/m²	27.7 ± 5.5	27.1 ± 5.0	28.1 ± 5.8	0.001	27.8 ± 5.4	28.4 ± 5.7	27.6 ± 6.2	28.4 ± 5.0	26.6 ± 4.8	<0.001
Heart rate, bpm	83.2 ± 21.7	86.1 ± 24.3	81.0 ± 19.1	<0.001	83.5 ± 22.3	80.8 ± 18.9	83.8 ± 22.2	90.1 ± 25.3	84.3 ± 24.9	<0.001
SBP, mmHg	123 ± 21	126 ± 23	120 ± 19	<0.001	123 ± 21	121 ± 19	121 ± 17	127 ± 23	127 ± 23	<0.001
Pulmonary rales, n (%)	677 (52.4)	309 (54.7)	368 (50.5)	0.14	514 (50.1)	235 (48.2)	49 (54.4)	89 (54.3)	138 (49.3)	0.45
Peripheral edema, n (%)	609 (56.9)	259 (58.1)	350 (56.0)	0.50	459 (54.4)	217 (52.5)	50 (62.5)	75 (58.6)	114 (52.1)	0.25
Elevated JVP, n (%)	293 (31.7)	135 (35.2)	158 (29.2)	0.052	217 (29.3)	94 (25.0)	21 (34.4)	42 (35.9)	59 (32.1)	0.064
NYHA class III/IV, n (%)	797 (61.4)	322 (56.8)	475 (65.1)	0.002	613 (59.6)	297 (60.7)	68 (75.6)	97 (59.9)	150 (52.6)	0.001
Orthopnea, n (%)	439 (33.2)	184 (31.6)	255 (34.5)	0.27	327 (31.2)	148 (30.0)	38 (41.8)	66 (39.3)	74 (25.3)	0.002
LVEF, %	26.2 ± 6.4	26.5 ± 6.3	26.0 ± 6.4	0.10	26.3 ± 6.2	25.9 ± 6.3	27.4 ± 5.4	26.1 ± 6.1	26.8 ± 6.2	0.078
HHF within 12 months before baseline, n (%)	447 (33.7)	169 (28.9)	278 (37.5)	0.001	346 (31.6)	181 (35.0)	35 (36.1)	44 (25.3)	86 (27.9)	0.032
Primary HF etiology, n (%)	-	-	-	0.12	-	-	-	-		0.12
Ischemic	574 (43.3)	242 (41.4)	332 (44.8)	-	429 (40.9)	216 (43.7)	34 (37.4)	59 (35.1)	118 (40.3)	-
Hypertensive	106 (8.0)	58 (9.9)	48 (6.5)	-	82 (7.8)	30 (6.1)	10 (11.0)	12 (7.1)	30 (10.2)	-
Valvular	73 (5.5)	33 (5.7)	40 (5.4)	-	61 (5.8)	31 (6.3)	4 (4.4)	6 (3.6)	20 (6.8)	-
Other/miscellaneous	572 (43.2)	251 (43.0)	321 (43.3)	-	477 (45.5)	217 (43.9)	43 (47.3)	91 (54.2)	125 (42.7)	-
Hemoglobin, g/dL	13.5 ± 1.8	13.5 ± 1.8	13.5 ± 1.8	0.91	13.7 ± 1.8	13.4 ± 1.8	13.4 ± 1.8	13.8 ± 1.8	13.7 ± 1.8	0.252
eGFR, ml/min/1.73m²	66.2 ± 20.7	65.5 ± 20.7	66.8 ± 20.6	0.23	67.7 ± 20.7	68.4 ± 20.4	66.9 ± 21.9	69.2 ± 20.0	65.8 ± 21.2	0.243
eGFR <45 ml/min/1.73m², n (%)	224 (16.9)	107 (18.3)	117 (15.8)	0.22	153 (14.6)	66 (13.4%)	14 (15.4)	19 (11.3)	53 (18.1)	0.17
Sodium, mmol/L	139 ± 4	140 ± 4	139 ± 4	0.015	140 ± 4	139 ± 4	140 ± 4	140 ± 4	140 ± 4	0.020
Potassium, mmol/L	4.2 ± 0.5	4.1 ± 0.4	4.2 ± 0.4	<0.001	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.5	4.0 ± 0.4	4.2 ± 0.4	<0.001

Potassium <4 mmol/L, n (%)	396 (29.9)	210 (36.0)	186 (25.1)	<0.001	658 (62.7)	114 (23.1)	29 (31.9)	73 (43.5)	88 (30.0)	<0.001
*Log*NT-pro BNP, ng/L	2.97 ± 1.31	3.06 ± 1.34	2.90 ± 1.29	0.031	2.85 ± 1.26	2.74 ± 1.25	2.84 ± 1.23	3.00 ± 1.32	2.94 ± 1.24	0.072
Hypertension, n (%)	756 (57.1)	317 (54.3)	439 (59.2)	0.070	603 (57.5)	301 (60.9)	59 (64.8)	91 (54.2)	152 (51.9)	0.030
Atrial Fibrillation, n (%)	562 (42.4)	249 (42.6)	313 (42.2)	0.88	426 (40.6)	197 (39.9)	39 (42.9)	67 (39.9)	122 (41.6)	0.93
Diabetes mellitus, n (%)	402 (30.3)	163 (27.9)	239 (32.3)	0.088	297 (28.3)	145 (29.4)	31 (34.1)	54 (32.1)	66 (22.5)	0.050
COPD, n (%)	220 (16.6)	97 (16.6)	123 (16.6)	0.99	166 (15.8)	75 (15.2)	13 (14.3)	26 (15.5)	51 (17.4)	0.83
Stroke, n (%)	119 (9.0)	50 (8.6)	69 (9.3)	0.64	86 (8.2)	43 (8.7)	5 (5.5)	10 (6.0)	27 (9.2)	0.46
PAD, n (%)	123 (9.3)	47 (8.0)	76 (10.3)	0.17	88 (8.4)	46 (9.3)	8 (8.8)	15 (8.9)	19 (6.5)	0.57
Device therapy, n (%)	336 (25.4)	116 (19.9)	220 (29.7)	<0.001	255 (24.3)	137 (27.7)	27 (29.7)	32 (19.0)	59 (20.1)	0.020
PCI or CABG, n (%)	411 (31.0)	156 (26.7)	255 (34.4)	0.003	306 (29.2)	165 (33.4)	23 (25.3)	42 (25.0)	74 (25.3)	0.036
Loop diuretic, n (%)	1319 (99.5)	582 (99.7)	737 (99.5)	0.70**	1044 (99.5)	400 (81.0)	59 (64.8)	130 (77.4)	204 (69.6)	<0.001
ACEi/ARB, n (%)	995 (75.1)	421 (72.1)	574 (77.5)	0.025	800 (76.3)	458 (92.7)	79 (86.8)	153 (91.1)	264 (90.1)	0.26
≥50% dose, n (%)*	681 (54.4)	328 (59.7)	353 (50.2)	<0.001	586 (55.9)	263 (53.2)	45 (49.5)	106 (63.1)	270 (58.0)	0.071
Beta-blocker, n (%)	1108 (83.6)	464 (79.5)	644 (86.9)	<0.001	889 (84.7)	473 (95.7)	84 (92.3)	159 (94.6)	274 (93.5)	0.41
≥50% dose, n (%)*	455 (36.3)	220 (40.1)	235 (33.4)	0.015	398 (37.9)	187 (37.9)	32 (35.2)	82 (48.8)	124 (42.3)	0.052
Digoxin, n (%)	250 (18.9)	95 (16.3)	155 (20.9)	0.032	188 (17.9)	90 (18.2)	20 (22.0)	31 (18.5)	36 (12.3)	0.072

*At V1 the up-titration period was the first 3 months. Patients who were lost to follow-up OR who died during the uptitration period were excluded from this analysis. For follow-up purposes only patients who completed the two visits were considered.

** Fisher exact test.

All variables have ≤10% missing values (except peripheral edema and jugular venous pressure, proportion of missing values are 19.2% and 30.3% respectively).

Legend: MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association; H, hospitalization; HF, heart failure; eGFR, estimated glomerular filtration rate; NT-pro BNP, n-terminal pro brain natriuretic peptide; COPD, chronic pulmonary obstructive disease; PAD, peripheral artery disease; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 2. Logistic regression: factors associated with and without MRA prescription at visit 1

Baseline		
Factors associated with MRA prescription	**Odds ratio (95% CI)**	**p-value**
Southern Europe countries	2.39 (1.87-3.05)	<0.001
BMI (per 5 kg/m² increase)	1.14 (1.02-1.28)	0.025
HHF in the 12 months before baseline visit	1.34 (1.04-1.73)	0.024
NYHA class III/IV	1.47 (1.16-1.88)	0.002
Device therapy	1.62 (1.22-2.15)	0.001
Hypertension history	1.30 (1.01-1.68)	0.044
Age (per 10 years increase)	0.79 (0.71-0.87)	<0.001
SBP ≥140 mmHg	0.55 (0.41-0.75)	<0.001
Potassium <4 mmol/l	0.59 (0.46-0.77)	<0.001

A backward conditional model was performed based on variables that have an association with a p-value <0.2 in Table 1 retaining in the final model the variable with a p-value <0.05.

Legend: MRA, mineralocorticoid receptor antagonist; BMI, body mass index; HHF, heart failure hospitalization; SBP, systolic blood pressure; NYHA, New York Heart Association; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 3. MRA prescription drop out and initiation from baseline to 9 months in the 1049 patients who completed the two visits

MRA (yes/no) n (%)	**MRA at Baseline** n=585 (55.9)	**No MRA at Baseline** n=461 (44.1)	**p-value**
MRA at 9 months n=662 (63.3)	494 (84.4)	168 (36.4)	<0.001
No MRA at 9 months n=384 (36.7)	91 (15.6)	293 (63.6)	

Legend: MRA, mineralocorticoid receptor antagonist.
The % presented are relative to the total of 1046 patients due to 3 (0.3%) missing values.

Table 4. Multinomial regression factors associated with MRA prescription change from baseline to 9 months (reference: MRA maintenance from baseline to 9 months)

MRA discontinuation (MRA at baseline but not at 9 months)	**Odds Ratio (95%CI)**	**p-value**
LVEF (per 5% increase)	1.27 (1.04-1.56)	0.020
NYHA class III/IV	2.04 (1.20-3.48)	0.009
PCI or CABG	0.58 (0.33-0.99)	0.047
MRA initiation (no MRA at baseline but prescribed at 9 months)	**Odds Ratio (95%CI)**	**p-value**
Heart rate (per 10 bpm increase)	1.16 (1.07-1.26)	0.001
Potassium <4 mmol/L	2.47 (1.66-3.66)	<0.001
SBP ≥140 mmHg	1.82 (1.16-2.86)	0.010
Southern Europe countries	0.52 (0.35-0.78)	0.001
No MRA (no MRA at baseline neither at 9 months)	**Odds Ratio (95%CI)**	**p-value**
Age (per 10 years increase)	1.37 (1.19-1.59)	<0.001
BMI (per 5 kg/m² increase)	0.78 (0.66-0.91)	0.002
NYHA class III/IV	0.68 (0.49-0.95)	0.022
Hypertension history	0.70 (0.49-1.00)	0.050

A backward was performed according to the type 3 analyses effect (global effect).

Legend: MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 5. Primary outcome associations for MRA therapy between V1 and V2

	Unadjusted HR (95%CI)	**p-value**	**Adjusted HR* (95%CI)**	**p-value**
No MRA (reference)	-	0.10	-	0.14
MRA baseline+9 months (yes)	1.00 (0.69-1.46)	0.99	1.02 (0.66-1.58)	0.93
MRA only baseline (yes)	1.80 (1.07-3.05)	0.028	1.68 (0.92-3.07)	0.092
MRA only 9 months (yes)	1.24 (0.78-1.97)	0.36	1.50 (0.89-2.53)	0.13

The 1049 patients who completed the two study visits were included in the analysis. Time was set from 9 months until the end of the study and events previous to 9 months were censored.

*adjusted on the clinical model derived from the BIOSTAT dataset that includes age, heart failure hospitalization in the last year, peripheral edema, systolic blood pressure, estimated glomerular filtration rate, urea, NT-pro BNP, hemoglobin, sodium, and use of beta-blocking agent at baseline.

Legend: MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval.